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# Feed Restriction in Rats

No CAS #

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Research and Testing

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In this study the effects of feed restriction (FR) and reduced body weight gain on various reproductive end points was evaluated (Chapin et al., *Fundam Appl Toxicol* 20:23–29 [1993]). The intent was to mimic the situation when animals in a toxicology study eat poorly and gain weight more slowly than controls. This study used Sprague-Dawley rats fed NIH-07 lab chow to maintain body weights of 90, 80, and 70% of ad libitum control body weight (CBW, see the introduction to the first mouse feed restriction study). The design was the same as the first mouse study: males and females housed separately and fed daily amounts of feed expected to maintain their body weights at target values. Males were tested for fertility at study weeks 8 and 15 by cohabiting with two unrestricted females/male. After the last mating, males were killed and necropsied. Females were evaluated for estrous cycle prior to, in the middle of, and at the end of the 15-week FR period. After the last smearing, females were each cohabited with a non-FR male, and killed on gestation day 14 to assess ovulation and implantation.

After a 5-week reduction period, body weights of FR rats remained  $\pm 5\%$  of target values.

No adverse clinical signs were noted. In neither male mating trial were any reproductive end points from the FR groups different from controls: number of litters per male, litter size, pup number and size were all equivalent across groups. At necropsy, male body weights were 88, 80, and 70% of controls. Absolute weights of liver, kidney, prostate, and seminal vesicles were reduced in all dose groups. Liver and prostate were reduced more than body weight, while kidney, epididymis, and seminal vesicles were less affected than body weight. Sperm concentration and shape were unaffected by FR, while the percent of motile sperm was reduced by the least and most FR, by 11 and 9%, respectively.

In FR females, killed on gestational day 14, there were no significant FR effects on the number of live or dead implants per litter. The number of corpora lutea was 20% lower in the 70% CBW females. The length and relative proportions of stages of the estrous cycle were not different across groups prior to and at the end of the FR period. At study week 8, the

most restricted group had a longer cycle: 5.18 days compared to the controls 4.25 days. This difference did not repeat at the end of the study. At necropsy, female body weights were 90, 81, and 66% of controls. Absolute liver and kidney weights were reduced in the middle and most restricted groups, while ovary weight was reduced only at 70% CBW. Relative liver weight did not differ across groups, while relative kidney weight was increased by 7 and 14% in the middle and most restricted groups, respectively. Histopathology was not performed for this study.

Thus, these data show that male rat fertility was never affected by FR sufficient to reduce body weight gain by less than or equal to 30%. Sperm parameters were effectively unchanged. For females, a small reduction in corpora lutea number at 70% CBW was seen as the only altered fertility parameter. In sum, the rat reproductive system appeared remarkably resistant to reduced body weight gain. If these data are replicable, it means that any adverse effects on reproductive end points seen in toxicity studies using rats are more likely to be a result of the test agent, and much less likely to be secondary to the reduced body weight.

# FEED RESTRICTION IN RATS

**Summary:** NTP Reproductive Assessment by Continuous Breeding Study.

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Chemical: **Feed Restriction**

CAS#: **NA**

Mode of exposure: **NA**

Species/strain: **Sprague-Dawley rats**

F <sub>0</sub> generation	Restriction levels→	90% BWT	80% BWT	70% BWT
General toxicity		Male, female	Male, female	Male, female
Body weight		↓, ↓	↓, ↓	↓, ↓
Kidney weight <sup>a</sup>		↑, —	↑, ↑	↑, ↑
Liver weight <sup>a</sup>		—, —	↓, —	↓, —
Mortality		—, —	—, —	—, —
Clinical signs		—, —	—, —	—, —

Reproductive toxicity, male mating trial 1			
̄x litters/male	—	—	—
# live pups/litter; pup wt./litter	—, —	—, —	—, —

Reproductive toxicity, male mating trial 2			
̄x litters/male	—	—	↑
# live pups/litter; pup wt./litter	—, —	—, —	—, —
Absolute testis, epididymis weight <sup>a</sup>	—, ↑	—, ↑	—, ↑
Sex accessory gland weight <sup>a</sup> (prostate, seminal vesicle)	—, —	—, —	—, —
Epidid. sperm parameters (#, motility, morphology)	—, ↓, —	—, —, —	—, ↓, —

Reproductive toxicity, female			
Estrous cycle length, prior to diet restriction	—	—	—
Estrous cycle length, during diet restriction	—	—	↑
Estrous cycle length, after diet restriction	—	—	—

Summary information
Affected sex? Unclear/Female
Study confounders: None

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change (p<0.05); —, —, no change in males or females. <sup>a</sup>Adjusted for body weight.